amended is limited to in vitro exposure of quiescent cells to the retroviral packaging cell line, thereby obviating that ground of rejection. Applicants note that claim 11 is already limited to such in vitro exposure.

The Office Action also states that claim 1 encompasses transformation of "any and all" quiescent cells that can be used in ex vivo treatment methods, and that such cells could encompass allogeneic, xenogeneic as well as autologous cells. The Office Action further states that it is not clear whether the method can be used for transforming any and all quiescent cells, such as senescent cells or non-hematopoietic quiescent cells. The Office Action states that some cells may require more than one growth factor to enter a new cycle of mitosis. Applicants respectfully disagree.

Applicants submit that the claimed method does not encompass the transformation of any cell that is not stimulated to divide by contact with growth factors. Claim 1 affirmatively states that "the surface bound growth factor induces the cells to divide." Because the claim thus requires that the target cell divides when stimulated by the surface bound growth factor, it clearly excludes those cells that do not divide when stimulated with growth factors, whether those cells are senescent or otherwise. Applicants therefore submit that the claimed method does not encompass the transformation of senescent cells.

Regarding the fact that some cell types require more than one growth factor to initiate a growth response, Applicants submit that the claims encompass the situation in which more than one growth factor is required to initiate a growth response. Applicants note that the specification, and indeed, the claims as filed and as currently pending, acknowledge the possibility that some cell types may require more than one growth stimulus. For example, on page 26, the specification states:

> Improved transduction rates using the method may be achieved using the synergistic action of additional cytokines. In this regard, SCF is particularly noted for its property of interacting in this way with other growth factors, which has led to the suggestion that on its own it may not be a mitogen but acts as an anti-apoptotic factor. To assess this, similar experiments to those described above

> can be performed using additional cytokines added to the media in conjunction with our modified producers. (page 26, lines 9-17)

Further, claim 12 as filed recited retroviral particles "wherein the particle displays multiple growth factors, and claim 4 as pending recites a cell line displaying multiple growth factors. Consistent with this claim 1 to recites "a growth factor". The claim thus covers the situations wherein both one growth factor and more than one growth factor is expressed on the surface of the cell line, and the growth factor or factors induce(s) the cell to divide. Applicants also note that in the above-quoted passage from page 26, the specification also makes it clear that in addition to the surface-bound growth factor, other growth factors can be added to the culture medium.

The Examiner suggests that the claims are not enabled because they encompass the transformation and transplantation of allogeneic and xenogeneic cells, and that these methodologies are unpredictable. With regard to transformation, Applicants submit that there is no question that one of skill in the art can substitute quiescent allogeneic or xenogeneic cells in the claimed transformation method, as long as the quiescent cells express a receptor for the growth factor expressed on the retroviral packaging cell. In fact, working Examples 1 and 2 show the transduction of human cells (TF-1 and primary human umbilical cord blood cells) using retrovirus produced by a murine retroviral packaging cell line, AM12, thereby demonstrating transformation facilitated by xenogeneic cells. Therefore, Applicants submit that claims 1-8 are fully enabled by the present specification. Applicants respectfully request the withdrawal of the §112, first paragraph rejection of these claims.

Regarding treatment claims 11 and 12, the Examiner suggests that these claims are overbroad because they encompass transplantation of allogeneic and xenogeneic cells, and that these methodologies are unpredictable. Applicants refer the Examiner to the holding of the Board of Appeals in Ex parte Mark, Bd. App., 1989, 12 U.S.P.Q.2d 1905.

In Ex parte Mark, the appealed broad claim was as follows:

> 1. A synthetic mutein of a biologically active native protein in which the native protein has at least one cysteine residue that is free to form a disulfide link and is

> nonessential to said biological activity, said mutein having at least one of said cysteine residues substituted by another amino acid and said mutein exhibiting the biological activity of said native protein.

The Mark specification set forth three working examples in which it was shown that each of three proteins have a non-essential cysteine residue which may be deleted or replaced, with the resulting mutein retaining biological activity. The Examiner in Ex parte Mark took the position that it would require undue experimentation to 1) construct "the innumerable muteins encompassed by" the claims and 2) to screen the muteins produced for any of those which exhibit biological activity after modification. The Board of Appeals in Ex parte Mark held that the Examiner's analysis was misguided, framing the relevant enablement issue as a question of whether, for a given protein having cysteine residues, one skilled in the art 1) would be able to substitute for or delete the cysteine residues as desired, and 2) could routinely determine whether deletion or replacement of cysteine residues in a given instance in fact resulted in an operative mutein falling within the claims.

Applicants submit that the Board's reasoning in Ex parte Mark is applicable to the present enablement rejection. The present Office Action raised the question of whether the specification supports a claim broad enough to encompass treatment involving transplantation of allogeneic and xenogeneic cells. Here, as in Ex parte Mark, the Examiner also suggests that undue experimentation would be required to practice the invention.

As noted above, Applicants' specification sets forth examples demonstrating the transformation of quiescent cells in vitro as claimed. The specification and the prior art provide guidance for the transplantation of autologous and allogeneic cells (see below). By applying the analysis of the Board of Appeals in Ex parte Mark to the enablement issues raised in the instant case, given the specification and the knowledge available in the art, one of skill in the art can 1) substitute allogeneic or xenogeneic quiescent cells for autologous cells in the claimed methods, and 2) readily determine whether such transplantation is effective, based, e.g., on the level of the polypeptide for treating a disease or disorder, changes in symptoms of the disease or disorder, and/or on the level of lymphocyte activation markers (e.g., soluble IL-2R) or rejection-related cytokines as was known in the art. Therefore, under analysis similar to that applied in Ex

parte Mark, claims 11 and 12 do not fail the enablement test merely because they encompass embodiments that may be inoperative.

As noted in the M.P.E.P. (2164.08(b), the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art (citing Atlas Powder Co. v. E.I. DuPont de Nemours & Co., 750 F.2d 1569, 1577, 224 U.S.P.Q. 409, 414 (Fed. Cir. 1984)). Applicants submit that this standard is satisfied by the present specification and knowledge available in the art at the time of filing.

First, the Examiner acknowledges that autologous cell transplantation is predictable. Second, regarding allogeneic cell transplantation, Applicants submit that the specification addresses the issue on page 9, lines 18-24, which discuss a means to reduce the immunogenicity of the packaging cells through co-expression of Fas ligand. In addition, in the Office Action response filed March 19, 2001, Applicants cited 6 prior art references demonstrating the availability of knowledge permitting the prevention of allogeneic transplant rejection in humans and 5 prior art references demonstrating similar knowledge in non-human allograft recipients. Therefore, given the specification and the knowledge available in the prior art, Applicants submit that one skilled in the art would be able to apply allogeneic cells in the methods of claims 11 and 12. The acknowledged possibility that xenogeneic cell transplants will be inoperative in the claimed treatment methods does not render the claims as a whole non-enabled because one skilled in the art can, using the specification and knowledge available in the art, readily determine whether such transplantation would be inoperative or operative with the expenditure of no more effort than is normally required in the art.

In view of the above, Applicants submit that the invention of claims 11 and 12 is enabled for the full scope of the claims, and respectfully requests that the §112, first paragraph rejection of these claims be withdrawn.

Rejection of Claims Under 35 U.S.C. §112, second paragraph:

Claims 1 and 11 are rejected under 35 U.S.C. §112, second paragraph as indefinite for reciting the phrases "the growth factor displayed on the surface of the cell line" or "the cell line carrying," because "it is not clear how a cell line can display on its surface because a cell has a surface not a cell line which is a collection of cells." Applicants submit that the amendment of claim 1 to refer to "a retroviral packaging cell" in place of " a retroviral packaging cell line" is sufficient to overcome this basis of rejection. The similar amendment has been made to claim 11.

Claims 1 and 11 are also rejected because the term "the cells" is said to be unclear because the claim recites a quiescent cell. Applicants submit that the amendment of "the cells" to "the quiescent cells" in claims 1 and 11 is sufficient to overcome this basis of rejection.

Claim 5 is rejected under 35 U.S.C. §112, second paragraph as indefinite for reciting the phrases "a viral envelope protein" and "a retroviral envelope protein" because it is not clear whether or not they refer to the same thing. Applicants submit that the amendment of claim 5 to recite "wherein said growth factor is expressed as an N-terminal fusion with a retroviral envelope protein" is sufficient to overcome this basis of rejection.

Claim 7 is rejected under 35 U.S.C. §112, second paragraph as indefinite because the phrase "the envelope protein" lacks antecedent basis in claim 1. Applicants submit that the amendment of claim 7 to change the dependency from claim 1 to claim 5 is sufficient to overcome this basis of rejection.

Claim 11 is rejected under 35 U.S.C. §112, second paragraph as indefinite because the phrase "surface bound growth factor" lacks antecedent basis. Applicants submit that the amendment of claim 11 to recite "so that growth factor is displayed bound on the surface of the retroviral packaging cell" is sufficient to overcome this basis of rejection.

In view of the above, Applicants respectfully request the withdrawal of each of the §112, second paragraph rejections.

Rejection of Claims under 35 U.S.C. §102:

Claims 1-4, 11 and 12 are rejected under 35 U.S.C. §102(b) as anticipated by Luskey et al., 1992, Blood 80: 396-402. The Office Action states that Luskey et al. teaches prestimulation of hematopoietic stem cells (HSCs) with stem cell factor (SCF) to increase retroviral-mediated gene transfer into the HSCs, and that prestimulated cells were cocultured with retroviral producer cells. The Office Action states that Luskey et al. teaches "that stromal cells(producer cells) express both membrane-bound and secreted SCF, although the level of protein expression is low." The Office Action concludes that claims 1-4 are anticipated because Luskey et al. teaches coculture of HSCs with retroviral producer cells that express a growth factor on their surface. Applicants respectfully disagree.

Applicants submit that Luskey et al. does not teach exposing target cells to a retroviral packaging cell expressing a recombinant nucleic acid encoding a growth factor so that the growth factor is displayed on the surface of the retroviral packaging cell, as required by amended claim 1. Specifically, the SCF expressed by the producer cells of Luskey et al. is endogenous to the cells, rather than recombinant, and, as acknowledged by both the Office Action and Luskey et al., "the level of protein expression is quite low." Because the Luskey et al. reference does not teach expressing a recombinant nucleic acid encoding a growth factor that is displayed on the surface of the retroviral packaging cell, the reference does not anticipate the invention of claim 1 or its dependents. For the same reason, Luskey et al. does not anticipate claim 11 as amended or claim 12 that depends from it. Claim 11 as amended also requires expression of a recombinant nucleic acid encoding a growth factor.

In view of the above, Applicants respectfully request the withdrawal of the §102 rejection of claims 1-4, 11 and 12 over Luskey et al.

Rejection of Claims under 35 U.S.C. §103:

A. Luskey et al. in view of Paul et al.

Claims 1 and 5-8 are rejected under 35 U.S.C. §103(a) as obvious over Luskey et al. in view of Paul et al. (U.S. Patent No. 5,736,387). The Office Action states that "Luskey et al. does not teach a fusion protein of the growth factor with a viral envelope protein wherein the growth factor is attached to the N-terminus of the retroviral envelope protein." Paul et al. is said by the Office Action to teach vectors wherein IL-2 encoding sequences are fused to the N-terminus of envelope sequences of amphotropic murine retrovirus or of ecotropic murine virus. The reference is also said to teach packaging cells transfected with such vectors, and that the fusion protein can be used to modulate targeted cells in accordance with the activity of the cytokine. The Office Action concludes that it would have been obvious to transform the producer cells of Luskey et al. with the envelope fusion vector of Paul et al. so that the producer cells express the envelope growth factor, because this would allow an increased amount of growth factor on the membrane of the producer cells, which would in turn facilitate infection of the HSC by the retroviral vector. Applicants respectfully disagree.

Applicants submit that Paul et al. teaches only producer cells in which the retrovirus that infects the target cell encodes the growth factor as an env fusion. Paul et al. does not, therefore, teach the situation in which the vector to be transduced does not encode a recombinant growth factor. Paul et al. therefore does not teach or suggest a retroviral packaging cell expressing a recombinant nucleic acid encoding a growth factor so that the growth factor is displayed on the surface of the retroviral packaging cell, the retroviral packaging cell carrying a vector comprising a nucleic acid encoding a polypeptide for treating a disease or disorder, wherein the vector does not encode the growth factor, as required by amended claim 1. Applicants submit that the amendment is supported by Examples 1-3, which each describe the transduction of quiescent cells with a retroviral vector that does not encode the recombinant growth factor expressed on the surface of the retroviral packaging cell line. Because Luskey et al. does not teach or suggest the expression of a recombinant growth factor on the surface of their producer cells, the combination of Paul et al. with Luskey et al. does not satisfy the requirements of claim 1 or of its dependents. Therefore, this combination of references does not render obvious the claimed invention. Applicants respectfully request the withdrawal of the §103 rejection of claims 1 and 5-8 over Luskey et al. in view of Paul et al.

B. Luskey et al. in view of Paul et al. and Lyman et al.

Claim 3 is rejected under 35 U.S.C. §103(a) as obvious over Luskey et al. in view of Paul et al. in further view of Lyman et al. The Office Action states that neither Luskey et al. nor Paul et al. teaches that the growth factor in the fusion protein is stem cell factor or flt3 ligand. The Office Action states that Lyman et al. teaches ligands for flt3 receptors that can induce the growth, proliferation and differentiation of progenitor cells and stem cells. Lyman et al. is also said to teach DNA encoding flt3 ligands, host cells transfected with cDNAs encoding flt3 ligands, methods of improving gene transfer to a mammal using flt3 ligands, methods of improving transplantation using flt3 ligand. The reference is also said to teach that a cDNA encoding flt3 ligands may be transfected into cells to ultimately deliver its gene product to the targeted cell or tissue. The Office Action concludes that it would have been obvious "to modify the retroviral vector of Paul (that encodes a fusion protein of a cytokine and a retroviral envelope protein) by cloning the flt3 ligand cDNA taught by Lyman et al., transfecting the vector into cells to produce packaging cells that would produce retroviral particles capable of infecting stem cells and affect their proliferation due to the expression of flt3 ligand and use these cells for transforming hematopoietic stem cells in the method of Luskey et al. with a reasonable expectation of success." Applicants respectfully disagree.

Applicants submit that Lyman et al. does not teach or suggest the recombinant expression of flt3 such that it is displayed on the surface of a retroviral packaging cell. Rather, Lyman et al. teaches that soluble flt3 ligand has advantages over membrane bound forms of the ligand, including ease of purification and better suitability for intravenous administration (see column 8, lines 7 to 61). Thus, not only does Lyman et al. not teach a retroviral packaging cell expressing a recombinant nucleic acid encoding flt3 ligand so that it is displayed on the surface of the retroviral packaging cell as required by claim 3 and amended parent claim 1, it teaches away from making a retroviral packaging cell expressing such a surface-bound version of flt3 ligand. As such, Lyman et al. does not remedy the deficiencies of Luskey et al. with regard to the invention of claim 3. Further, Lyman et al. does not remedy the deficiency of Paul et al., namely the lack of a teaching of a vector comprising the nucleic acid encoding the polypeptide for

treating a disease or disorder wherein the vector does not encode the growth factor, as required by claim 3 and amended parent claim 1. Because Lyman et al. does not remedy the deficiencies of either Luskey et al. or Paul et al. with regard to claim 3 or parent claim 1 as amended, the combination of these references cannot satisfy the requirements of claim 3. Therefore, the combination cannot render obvious the invention of claim 3. Applicants respectfully request that the §103 rejection of claim 3 over these references be withdrawn.

In view of the amendments made herein and the accompanying remarks, Applicants submit that all issues raised by the Examiner in the Office Action have been addressed. Applicants therefore respectfully request the reconsideration of the claims.

Respectfully submitted,

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Version with markings to show changes made:

1. (Twice Amended) A method of transforming a population of quiescent cells with a nucleic acid encoding a polypeptide for treating a disease or disorder, the method comprising:

exposing [the] a population of quiescent cells in vitro to a retroviral packaging cell [line] expressing nucleic acid encoding a growth factor so that the growth factor is displayed on the surface of the retroviral packaging cell [line], the retroviral packaging cell [line or retroviral particles] carrying a vector comprising the nucleic acid encoding the polypeptide for treating the disease or disorder, wherein said vector does not encode said growth factor, and

wherein the surface bound growth factor induces the quiescent cells to divide, so that the nucleic acid encoding the polypeptide for treating a disease or disorder can incorporate into the genome of the cells.

5. (Amended) The method of claim 1 wherein said [the] growth factor is expressed as [a] an N-terminal fusion with [a viral envelope protein and is attached to the N-terminus of] a retroviral envelope protein.

7. (Amended) The method of claim [1] 5 wherein the retroviral envelope protein is viral envelope SU protein.

11. (Twice Amended) A method of treating a patient having a disease or disorder, the method comprising the steps of:

a) exposing a population of quiescent cells to a retroviral packaging cell [line] in vitro, said retroviral packaging cell [line] expressing a recombinant nucleic acid encoding a growth factor so that the growth factor is displayed on the surface of the retroviral packaging cell [line], the retroviral packaging cell [line or retroviral particles] carrying a vector comprising a nucleic acid encoding a polypeptide for treating said disease or disorder, wherein the surface bound growth factor induces the quiescent cells to divide, so that the nucleic acid encoding the polypeptide for treating said disease or disorder can incorporate into the genome of the cells; and

b) administering to the patient an amount of the cells of step (a) effective to treat said patient's disease or disorder.